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Editorial Comment

Pathogenetic Mechanisms of Coronary Artery Spasm*

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Coronary artery spasm was first proposed as a cause of spontaneous, recurring anginal attacks over a century ago (1). Because this brilliant clinical intuition could not be demonstrated at postmortem study, it fell into progressive disrepute until, in the early 1950s, coronary artery spasm was considered "the resort of the diagnostically destitute" (2). In 1959, the notion of coronary artery spasm was bravely resurrected with clinical acumen by Prinzmetal et al. (3), and it became a proved hypothesis in the mid-1970s (4).

Dynamic coronary artery stenoses caused by increased coronary tone, thrombosis or their combination are now recognized components of stable and unstable ischemic syndromes (5–8). Yet coronary artery spasm, as most typically observed in variant angina, appears to be a rare condition with some rather unique features: it is usually localized to a segment of epicardial coronary artery and causes transmural myocardial ischemia typically manifested by ST segment elevation, as documented during continuous electrocardiographic (ECG) monitoring. Coronary spasm tends to be transient and is usually promptly relieved by immediate administration of nitrates. In variant angina, it is usually episodic; patients may experience a waxing and waning of the disease for weeks, months and even years as spasm occurs spontaneously. Coronary spasm can be reproduced by ergot derivatives and by hyperventilation. Many variations of this classical clinical picture can be encountered, and it would be unwise to consider any single pathogenetic mechanism responsible for the whole spectrum of ischemic syndromes related to abnormal coronary vasoconstriction.

The present study. In this issue of the Journal, Hoshio et al. (9) conclude that "a coronary vasomotion disorder, which involves increased basal coronary artery tone and hyperreactivity to vasoconstrictive stimuli, not only at a localized segment but also of the entire coronary artery tree, is present in patients with vasospastic angina." In our opinion, this conclusion requires qualification.

The most striking finding in their study is the magnitude of coronary vasodilation observed proximal to the "spastic" segments and also in nonspastic arterial branches in the "vasospastic angina" group after the administration of nitrates. Although confined to the "spastic" segments, marked dilation had been previously observed after nitrate administration in one study of white patients with typical variant angina (10), but not in others (11,12). Marked dilation of "nonspastic" segments after nitrates, however, was not previously observed in typical forms of variant angina, although it was noted occasionally in patients with other forms of coronary constriction (Fig. 10 of Maseri [5]). The extent of dilation observed in nonspastic segments in the Japanese "vasospastic angina" group is nearly double that commonly reported in whites (10–15). The extent of dilation found in the Japanese "nonvasospastic angina" group, however, is slightly less than that found in whites (13–15). The extent of coronary constriction caused by ergonovine in whites is nearly double that in the Japanese control group, and of the same order of magnitude as that observed in nonspastic segments of the "vasospastic angina" group (16–18).

The findings of Hoshio et al. (9) should be considered in the light of the type of patients included in their "vasospastic angina" group. Unfortunately, insufficient information is provided on the clinical characteristics of their patients, such as type of angina, presence of spontaneous ST segment elevation during continuous ECG monitoring and results of exercise testing. It is of importance that only 13 of their 30 patients with vasospastic angina developed ST segment elevation during ergonovine administration. Moreover, their criterion for defining coronary spasm (50% reduction of diameter, localized or diffuse) probably allowed the inclusion of patients (such as the one presented in Figure 10 of Maseri [5]) who had no classical clinical features of variant angina and did not develop angina or ST segment elevation despite marked diffuse coronary constriction observed during ergonovine administration. Because data on individual patients are not presented in the study of Hoshio et al. (9), it is impossible to ascertain how many of the patients who developed ST segment elevation with ergonovine (and therefore had at least one typical feature of variant angina) behaved like the average of the group. It is conceivable that their study patients as a whole are somewhat different from the patients with variant angina most commonly encountered in Western countries. The dilation of nonspastic arterial segments caused by nitrates in their patients is of such a magnitude that it could not have passed unnoticed, if

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present, in white patients with variant angina. The conclusion reached by Hoshio et al. certainly applies to the type of patients who were more prevalent in their possibly heterogeneous study group, but it should not therefore be extrapolated to all patients with variant angina. Thus, we have some reservations as to the diagnostic value and ability of the angiographic findings described by Hoshio et al. (9) to predict the occurrence and location of coronary artery spasm in patients with variant angina.

Pathogenesis of coronary artery spasm. After coronary artery spasm became a proved cause of variant angina, many pathogenetic hypotheses were put forward to explain the origin of this syndrome. Unfortunately, none has managed to stand the test of time. As suggested in 1976 (19), any pathogenetic hypothesis of variant angina should fit simple, common clinical observations such as the usual recurrence of spasm at the same arterial site and the possibility of reproducing spasm by a number of pharmacologic and physiologic tests that indicate a localized alteration of the arterial wall and a local susceptibility to constrictor stimuli.

According to the geometric theory of MacAlpin (20), a rationalization of Prinzmetal's original hypothesis, spasm could result from the amplification of normal coronary constriction by a subintimal plaque. However, this hypothesis was not supported by quantitative measurements in patients with variant angina (21) or in pigs, the closest animal model of the syndrome (22). Although, in variant angina, spasm usually develops at the site of an angiographically detectable plaque, it may also occur in arteries with no detectable obstructive plaques at angiography or even at postmortem study (23). The prevalence of angiographically normal arteries in patients with variant angina appears to be higher among Japanese patients than among whites. The frequency of completely normal coronary arteriograms has ranged from 0% to 24% in American and European studies, whereas >50% of patients in Japanese studies have angiographically normal coronary arteries (23–29). This potentially intriguing difference suggests the need for a study of carefully characterized and clinically matched groups of patients from the two ethnic groups.

An active alteration that makes a segment of coronary artery wall particularly hyperreactive to constrictor stimuli must be postulated as a pathogenic mechanism of coronary spasm, and, indeed, a localized segmental hyperreactivity also seems to be present in the patients described by Hoshio et al. (9). We have observed (11) a local coronary hyperreactivity in response to intracoronary ergonovine and have also shown (30) that it is not specific for one type of stimulus-receptor interaction. This hyperreactivity could result from alterations of the endothelium, arterial smooth muscle or adventitia.

Conclusions. We believe that for the time being it is reasonable to assume that coronary vasoconstriction and even typical coronary artery spasm can be caused by more than one mechanism. Thus, it is wise to continue to patiently collect established facts rather than accept "unifying" pathogenetic hypotheses. Lumping together patients who may be heterogeneous could confuse rather than clarify the issue of the pathogenetic mechanisms of coronary artery spasm. It is hoped that properly collected data will eventually all fit together like the tesserae of a mosaic to form a meaningful pattern.

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